New directions in MEN1 management: navigating the new clinical practice guidelines, Papalou and Korbonits (2025). European Journal of Endocrinology; 193:R71-R82, https://doi.org/10.1093/ejendo/lvaf247

Multiple endocrine neoplasia type 1 (MEN1): recommendations and guidelines for best practice, Brandi et al (2025). Lancet Diabetes and Endocrinology; 13: 699-721, doi: 10.1016/S2213-8587(25)00119-6

- **Background:**

"Multiple endocrine neoplasia type 1 (MEN1) remains a clinically challenging syndrome due to its genetic heterogeneity, variable penetrance, and lifelong surveillance needs. The newly published 2025 MEN1 guidelines introduce important refinements in managing this complex hereditary syndrome, reflecting 2 decades of accumulated clinical experience and molecular insights. This review provides a concise overview of these recommendations and a systematic comparison with the previous MEN1 guideline as well as other recent international guidelines. This comparison points out fundamental advances in genetic interpretation, risk stratification, and therapeutic decision-making, highlighting both the progress towards standardization and the persistent controversies that underscore the complex interplay between evidence, pragmatism, and individualized care. The novel guidelines show essential directions for future research in MEN1." (from Papalou and Korbonits, 2025)

- **Aim:**

Papalou and Korbonits (2025) present a helpful summary of the latest MEN1 best practice guidelines (Brandi et al, 2025). The former is half the length of the latter and presents some of the recommendations in the form of diagrams and tables, making for easier reading. Papalou and Korbonits also compare these guidelines with analagous French and American guidelines.

- **Methods:**

The 2025 guidelines (Brandi et al, 2025) employed a more rigorous methodology than their predecessors, utlising a structured Delphi consensus process and incorporated systematic reviews to address key clinical questions. The aim was to strengthen the evidence base for recommendations in areas previously guided largely by expert opinion.

- **Results:**

The diagnostic criteria for MEN1 remain largely unchanged, though with some nuanced refinements, including attempts to classify 'mutation-negative' MEN1 or MEN1-like phenotypes to guide surveillance and management in those cases. There are also refinements to recommended genetic testing criteria with age of onset cut-offs for the various manifestations such as primary hyperparathyroidism (PHPT), pituitary and neuroendocrine tumours (NETs). A

less stringent approach is recommended in terms of when to proceed to genetic testing for children at risk of inheriting MEN1 pathogenic variants (PV). Testing is recommended in the first decade of life rather than before five years of age as previously recommended. Surveillance in children and adults with MEN1 PVs is nicely illustrated in Figure 2 of Papalou and Korbonits's paper. Standardised approaches to therapy for each tumour type are recommended. Some controversies are acknowledged to remain:

- Timing of testing: whether decade-of-life genetic screening optimally balances early intervention versus psychological burden.
- Somatic variant implications: how to manage patients incidentally found to harbour somatic MEN1 mutations.
- Imaging controversies: the recommendation for CT-based thymic NET surveillance—while sensitive—sparks concern about cumulative radiation exposure in this young population.

❖ **Conclusions:**

"The 2025 MEN1 guidelines represent a significant evolution in managing this complex syndrome, offering clearer genetic testing frameworks, refined surveillance protocols, and more standardized therapeutic approaches—particularly for paediatric populations. While these advances address long-standing clinical uncertainties, persistent controversies surrounding optimal screening intensity, genetic testing strategies and imaging modalities underscore the need for prospective, international collaborative research. As precision medicine advances, future iterations must balance emerging evidence with the practical realities of MEN1 care, ensuring guidelines remain both scientifically rigorous and clinically actionable. Their ultimate success will be measured not just in consensus statements, but in improved outcomes for this vulnerable patient population." (from Papalou and Korbonits, 2025)

❖ **Reflections for practice:**

I personally found the summary from Papalou and Korbonits very helpful, working in the specialist field of endocrine neoplasia genetics. The main issue with the latest guidelines I have is the recommended approach for children at 50% risk of having PVs being referred to paediatric endocrinology in the first instance in the first decade of life for the family to have a discussion around clinical symptoms and then consider genetic testing downstream to this. This contrasts with my own current practice (and that in my centre) of arranging genetic testing in the first instance before referring to paediatric endocrinology only the PV positive children for clinical review and surveillance. Referring to paediatric endocrinology before genetic testing would lead to a doubling in referrals to that speciality, who may not have the resources to manage these patients and 50% of these patients will test negative for the PV in any case.

The genetic testing 'in the first decade of life' seems like a sensible strategy and I wonder if specialised (endocrine-focused) genetic counselling could ensure that families can have the necessary information around symptom awareness prior to genetic testing closer to the age of 10 ahead of referral to paediatric endocrinology if PV positive.

Prevalence of the Predisposing Gene MBD4 for Uveal Melanoma, Anais et al., 2026. JAMA Ophthalmology, doi:10.1001/jamaophthalmol.2026.1071

Introduction

- *MBD4* germline pathogenic and likely pathogenic variants have recently been identified to predispose to uveal melanoma (rare intraocular tumour)
- The aim of this study was to assess the risk of developing uveal melanoma for carriers of the *MBD4* monoallelic germline pathogenic variant

Methods

- 896 patients diagnosed with uveal melanoma at eh Institut Curie (France), had germline genetic testing for a panel which included *BAP1* and *MBD4*
- Variant classification was carried out according to the ACMG and Genomics and Association for Molecule Pathology

Results

- 23/896 individuals carried an *MBD4* germline LP/P variant. 7 of these were previously reported by the team.
- The number of *MBD4* carriers exceeded the number of *BAP1* carriers
- All 11 tumours in the *MBD4* germline P/LP carriers analysed for CNVs presented with monosomy 3, with loss of *MBD4*. 5/11 tumours also carried a somatic *BAP1* deleterious mutation.
- The median age at uveal melanoma diagnosis in the 8 *BAP1* LP/P variant carriers, was 47 years. This was not different from the age of diagnosis of the rest of the uveal melanoma cohort.

Discussion

- This study showed the importance of *MBD4* as an important predisposition gene to uveal melanoma, in the French population. This is consistent with the description of familial and multiple uveal melanoma cases.
- The prevalence of germline *MBD4* P/LP variants supports a strategy of broad patient screening given the therapeutic and genetic counselling implications
- Further work is needed to determine the significance and prevalence across other populations

Limitations

- The comparison was with non-Finnish European gnomAD controls, as there is no large series of control French individuals available
- The high incidence may not be generalisable for all populations of European ancestry

Genome sequencing of Undiagnosed European Patients Suspected of Hereditary Cancer: Diagnostic Yield and Identification of Candidate Causative Variants, *JCO Precision Oncology*, Martins et al. 2026, DOI: 10.1200/PO-25-00354

Introduction

Solve-RD project aimed to provide genetic diagnoses for unsolved patients with rare disease. They used short-read WGS on 98 unsolved unrelated patients with suggestive hereditary cancers, but no prior genetic diagnosis.

Methods

- Patients were selected based on clinical criteria defined by ERN GENTURIS Solve-RD Data Interpretation Task Force to identify individuals with strong clinical suspicion of hereditary cancer:
    1. Multiple primary cancers in 4 or more organs or 3 or more if two were rare
    2. Adult-type cancers diagnosed at age ≤ 25
    3. ≥ 50 GI adenomatous polyps dx at ≤ 50, OR ≥ 50 of any histology at ≤30 years
- 98 patients were recruited from ERN GENTURIS reference centres
    - 90 patients had previous non-informative multigene, exome or single-gene analyses.
    - 8 had not undergone testing because of local eligibility restrictions
- WGS, MSI, IHC for MMR proteins and RT-qPCR were conducted.

Results

- Clinical characteristics of the patients
    - Median age at first cancer or polyposis diagnosis was 23.5 years
    - Females comprised 74% of the cohort
    - In total, 166 cancer diagnoses were reported, representing 43 unique tumour phenotypes. Breast cancer was the most frequent, accounting for 23.5% of all diagnosis.
    - Criterion 1 showed the highest phenotypic diversity, with 28 of 43 tumour types and criterion 3 showed the lowest phenotypic diversity, with only three phenotypes observed (polyposis, colorectal cancer, uveal melanoma)
- Pathogenic variants in Phenotype-Associated Hereditary Cancer Genes
    - Pathogenic or likely pathogenic variants in hereditary cancer genes matching the clinical phenotype were identified in 6% of the cohort:

Criterion	Gene	Patient phenotype
	TP53 germline PV	Lung adenocarcinoma at 57 years, leiomyosarcoma at 55 years, breast cancer at 67 years and multiple myeloma at 68 years

1	BAP1 LP germline variant	Vulvar cancer (36 years), hepatocellular cancer (45 years), anal cancer (55 years), chromophobe renal cancer (73 years), bladder cancer (69 years) and eye tumour
2	TP53 pathogenic mosaic variant (27% VAF)	Breast cancer at 23 years TP53 with a VAF of 27% so likely somatic mosaicism Also carried FANCM LP variant
	Patient also had a FANCM likely pathogenic germline variant	
	BARD1 Likely pathogenic germline variant	2 breast cancers at age 22 and 38 years
3	APC pathogenic variant (mosaic) 10% VAF	adenomatous polyposis (47 years)
	MBD4 likely pathogenic germline variant	Polyposis (50 years), colorectal cancer (52 years) and uveal melanoma (61 years)

Potentially relevant SNVs and Indels and PV in non-phenotype associated or low-penetrance genes

- *ERCC3* variant which has been associated with low/moderate breast cancer risk. This patient was also heterozygous for *FANCM* VUS.
- *MSH6* LP variant in a 19M with papillary thyroid cancer. IHC was inconclusive, but they did have a 2nd degree relative with endometrial cancer showing MSH6 protein loss.
- *ATM* and *BRIP1* VUS' identified in two patients with invasive ductal breast cancer in their early 20s.
- *FANCM* variant in a patient with ovarian cancer at 21 years, breast cancer at 56 years and colorectal cancer at 61 years. The multi-tumour phenotype suggests potential additional genetics or nongenetic risk factors.
- *SDHA* LP variant found in a 46 year old patient with adenomatous polyposis and *FANCA* LP variant in a 14 year old patient with polyposis. Neither phenotypes are associated with the gene. Due to *SDHA*'s low penetrance and the uncertain role of heterozygous *FANCA* variants in cancer predisposition, the variants were not reported to the patients.

Structural variants of potential interest

- An inversion was found on chromosome 3, in a patient diagnosed with clear cell renal cell carcinoma, two lung cancers, and gastric carcinoma with lymphoid stroma which is a subtype associated with somatic DNA MMR deficiency. The inversion affects *VHL* and *MLH1* , which may elevate gastric cancer risk and clear cell renal cell carcinoma
- Eight additional rare chromosomal inversions involving one of 127 hereditary cancer genes were identified in eight patients. Three had breakpoints in intergenic regions and five disrupted genes not previously linked to cancer.

- Two young patients with breast cancer had an inversion affecting the same genomic region on chromosome 2, which includes *ERCC3*, associated with moderate risk of breast cancer.

Noncoding variants in phenotype-specific hereditary cancer genes

- Several variants were considered of particular interest because of their gene-phenotype concordance: *BRIP1* promoter variant in 20y with breast cancer, *RAD51C* enhancer variant in a 25y with ovarian cancer, and potentially regulatory *NF1* enhancer variant in a patient with multiple tumours, *CDH1* regulatory variant in a patient with breast cancer and epithelioid hemangioendothelioma, *BMPR1A* enhancer variant in a 35y patient with adenomatous polyposis

Discussion

- Several factors may explain why standard testing missed diagnoses; low-level mosaicism filtered out because of VAF thresholds, involvement of newly recognised or rarely tested genes, reclassification of variants as pathogenic, undetectable SVs/CNVs in panel testing, coverage gaps and incomplete clinical data
- A potential mosaic *TP53* PV was found in patient with breast cancer, who was only tested for *BRCA1/2* in the panel test. *APC* mosaicism was found in a patient with polyposis, but was missed in previous testing due to the low VAF. Compared to WGS, gene panel testing with relaxed or no VAF filters, is more effective for detecting mosaicism because of higher coverage depth.
- Patient with adenomatous polyposis was found to have a pathogenic *APC* variant in all three polyps and normal mucosa, but not in blood. This suggests the importance of targeting tissue testing in patients with unexplained adenomatous polyps, as APC mosaicism is common.

Conclusion

- Resequencing patients with no genetic diagnosis but a strong phenotype, increased the yield by 6%, with an additional 5% showing variants of high interest. The approach enabled identification of coding gPVs, as well as candidate coding and noncoding variants and SVs in phenotype-associated genes. To validate the relevance, further tumour mutational analyses, co-segregation studies and functional assays are essential.
- They recommend reanalysis or resequencing of unresolved cases, incorporating both coding and non-coding regions, with particular attention to SVs, postzygotic mosaicism and deep intronic splicing altering variants.

Monthly Journal Round-Up brought to you by:

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